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RECEIVED 26 February 2026

REVISED 13 May 2026

ACCEPTED 27 May 2026

PUBLISHED 11 June 2026

CITATION

Boukraâ D, Aribi R, Başar Y, Tabti S,
Tadjeddine N, Fergoug T, Alfaleh AA,
Altalhi R, Alnajeebi AM, Banjer HJ,
Almehmadi A, Helal M, Alaoufi SH and
Sami R (2026) Optimizing drying
technologies for *Salvia officinalis* L.:
balancing essential oil yield,
phytochemical integrity, and
computational prediction of antioxidant
synergy.
Front. Sustain. Food Syst. 10:1818527.
doi: 10.3389/fsufs.2026.1818527

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Tadjeddine, Fergoug, Alfaleh, Altalhi,
Alnajeebi, Banjer, Almehmadi, Helal,
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Optimizing drying technologies for *Salvia officinalis* L.: balancing essential oil yield, phytochemical integrity, and computational prediction of antioxidant synergy

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Salvia officinalis L. is an important aromatic and medicinal plant with essential oil (EO) quality that can be significantly affected by post-harvest processing. The aim of this study is to determine the drying temperature of *S. officinalis* L. suitable to maximize essential oil (EO) yield and to preserve physicochemical properties, antioxidant potential, and phytochemical profile. A complementary in silico study was extended to estimate the binding combinations of EO contents toward antioxidant-related enzymes. Fresh leaves were dried in oven drying (50 and 80 °C), and by freezing (-20 °C). Results demonstrated that the maximum yield was achieved with 50 °C (0.29%), compared with the fresh sample (0.16%). Significant variations cross this chemotype have been shown depending on the drying temperature. Increases of limonene (25.8 and 25.5%) against a decrease in α -Thujone (13.3 and 13.3%) were observed at 50 °C and -20 °C, respectively. Higher antioxidant activity with IC₅₀ achieving (2.4 and 2.5 μ g/mL) was observed 50 °C and -20 °C, respectively. Molecular docking simulations efficiency of major constituents against antioxidant enzymes showed that most molecules, particularly epiglobulol, exhibited cytochrome P450 (CYP₂) substrate activity with MM-PBSA free energy results (-15.90 $\pm$ 0.25), suggesting that these molecules have the ability to initiate antioxidant mechanisms. According to these results, drying at 50 °C and freezing at -20 °C appear to be the most effective temperature for preserving chemical integrity and functional properties of *S. officinalis* EO. These

findings provide valuable information for optimizing post-harvest processing of *S. officinalis* and support the potential use of its essential oil in sustainable food, pharmaceutical, and cosmetic applications.

KEYWORDS

antioxidant capacity, binding energy, drying temperature, molecular docking, *Salvia officinalis* L., volatile compounds

Introduction

Aromatic and medicinal plants are important sources of bioactive substances, including EO, which is highly valued for its antioxidant and therapeutic traits (Raal et al., 2024). Preservation of bioactive compounds presents a key concern for both scientific research and industrial applications (Maddaloni et al., 2025). Volatile constituents are sensitive to environmental and management conditions, and post-harvest processing, particularly drying, plays a pivotal role that influences their quality (Boukraâ et al., 2024).

Drying is the most widely used preservation technique for herbal plants. Beyond reducing moisture to prevent microbial spoilage, it plays a decisive role in influencing the rate and composition of secondary metabolites (Nakra et al., 2025). Selected technique and optimal temperature can markedly influence both essential oil yield and chemotype (Boukraâ et al., 2021). Parameters, such as temperature, duration, and airflow interact with the structural and physiological characteristics of plants, triggering loss, transformation, degradation of aromatic compounds, and altering functional properties (Ghamgui et al., 2026). Conversely, controlled or optimal-temperature drying approaches have been shown to better preserve the integrity and bioactivity of key volatile compounds (Mina et al., 2025). In this instance, controlling drying conditions by optimizing drying temperatures and time to simultaneously maintain or maximize essential oil yield and ensure economic efficiency remains a key challenge (Ashtiani and Martynenko, 2025).

Currently, research increasingly focuses on identifying EO yield and key functional properties using analytical and computational tools, including GC–MS profiling, chemometric analyses, and molecular docking (Kulak et al., 2026; Temel et al., 2026). These techniques deeply evaluate the mechanisms by which drying conditions influence the stability and performance of bioactive compounds (Tabti et al., 2025). This growing knowledge supports the development of high-value EO and informs best practices for the post-harvest processing of essential oil-bearing plants.

Salvia officinalis L. (sage), belonging to the Lamiaceae family, has long been associated with tonic, antiseptic, carminative, and antihydrotic properties (Imran et al., 2024; Thorat et al., 2025). This plant is distinguished by its wide range of biological activities, attributed to its richness in phenolic components, particularly terpenoids (Bouzabata et al., 2026). Obviously, *S. officinalis* EO has attracted considerable interest across the Mediterranean regions, where the species is extensively cultivated and benefits economically from its commercialization due to its aromatic profile and its potential applications as a therapeutic agent (El Euch et al., 2019; Khedher et al., 2017).

This experiment was designed to assess essential oil yield, phytochemical components, and antioxidant activity at different drying

temperatures. Additionally, computational (*in silico*) analysis was conducted to calculate the interaction between major volatile molecules and key antioxidant activity-related enzymes.

Materials and methods

Salvia officinalis was collected in March 2024 from the Mascara region in Algeria. Botanical identification was performed by Dr. Amroune Mohamed, an agronomic researcher at Mustapha Stambouli University, Mascara, Algeria. Leaves were cleaned and subjected to oven drying at two drying temperatures (50 and 80 °C), freezing at −20 °C, and fresh leaves were used as the control.

Hydrodistillation

Essential oil (EO) recovery was extracted using the Clevenger method for 4 h (Durling et al., 2007). Afterward, EOs were stored in amber glass vials at 4 °C to prevent photo-oxidation and maintain composition integrity.

The yield of EO was determined using Equation 1.

$$\text{EO Yield (\%)} = \left[\left(\text{EO mass} / \text{Initial Plant Mass used} \right) \times 100 \right] \quad (1)$$

Physicochemical analyses

Determination of density, refractive index, and UV–Visible spectral analysis were studied, according to standard analytical methods.

The density was measured at 20 ± 0.5 °C using a pycnometer, in accordance with AFNOR (NFT 75–111) standards. The density was expressed using the Equation 2:

$$De = \frac{m_2 - m_0}{m_1 - m_0} * De_{H_2O} (20^\circ C) \quad (2)$$

Where m_0 , mass of the empty pycnometer; m_1 , mass filled with H_2O ; and m_2 , mass filled with essential oil.

Measurement of refractive index was conducted at 20 °C by an electronic refractometer (Abbe 1 T/ 4 T), AFNOR (NFT 75–112) standards. The results were calculated using Equation 3:

$$n_{20} = nt + (t - 20)^* (0.00045) \quad (3)$$

Where: nt is the refractive index measured at temperature t.

UV–Vis spectra were measured using a UV–Visible spectrophotometer (mini 1,240, CAT No 206–55658–38, SERIAL No

A10934336690CS, frequency 220 V-240 V-50/60HZ 160VA) in the wavelength range of 200–400 nm and 400–800 nm. Absorption peaks were analyzed to identify characteristic chromophoric groups and to assess the purity and stability of major constituents (Semeniuc et al., 2018).

Gas chromatography analysis

Identification and quantification of EO compounds were completed using a gas chromatography apparatus coupled with mass spectrometry (GC–MS) (on a TQ8030 GCMS–Shimadzu, Japan) on an Agilent Technologies GC7890A system coupled to a 5975C triple axis mass spectrometer and mounted with an HP-5MS capillary column (30 m × 250 µm × 0.25 µm). Following standard operating parameters, a 0.1-µL sample was injected with the injector set at 250 °C. Helium (He) served as the carrier gas at a constant flow frequency of 1.0 mL/min. The oven temperature program was initiated at 50 °C (kept for 3 min), then intensified to 5 °C/min to 220 °C, and held for 10 min, resulting in a total runtime of 34 min. The identification of EO components was achieved through comparison of their retention indices (RI) and relating mass spectra against authentic standards and NIST reference data (National Institute of Standards and Technology) (WebBook, 2021). Relative percentage of each constituent was determined based on their corresponding GC maximum areas, using retention indices and a normalization method. Major and minor constituents were subsequently classified according to their chemical families, including monoterpenes, sesquiterpenes, phenolic derivatives, etc.; (Erenler et al., 2016).

Radical scavenging activity determination

The antioxidant activity of EO was determined using the DPPH method (Awika et al., 2003). Different dilutions of the EO from the various samples were prepared in methanol at concentrations of 1, 0.5, 0.25, 0.125, and 0.06%. Two standard antioxidant solutions, based on ascorbic acid and tannic acid, were also prepared for comparison. 2,2-Diphenyl-1-picrylhydrazyl (DPPH) solution was freshly prepared by dissolving 0.004 g in 100 mL of methanol. Successive dilutions were made until the absorbance value of the solution ranged between 0.9 and 1.0.

50 µL of each sample was added to 1.950 mL DPPH. The negative control consisted of 50 µL of methanol. All mixtures were incubated in the dark at room temperature for 30 min to minimize photo-degradation. The absorbance was read at 517 nm. The percentage of RSA was calculated using Equation 4:

$$\text{RSA (\%)} = \left(\frac{A_o - A_s}{A_o} \right) * 100 \quad (4)$$

Where A_o is the control absorbance and A_s is the sample absorbance.

The IC_{50} value of the sample was calculated graphically based on a linear regression equation obtained by plotting concentrations against RSA. Lower IC_{50} values indicate stronger antioxidant potential and greater free radical scavenging efficiency of the EOs.

Molecular docking simulation

These studies are computational-based methods used to predict target protein binding affinities that interact energetically with ligands (Panigrahi and Sahu, 2025). This analysis was accomplished using Auto DockVina tools version 4.2 programs (Başar et al., 2024). The application of Discovery Studio Visualizer 2021 was used to visualize and analyze the docking poses with the lowest interaction energies (Tekel et al., 2025).

The 2D structures of the main volatile compounds in the plant *S. officinalis* were downloaded from NIST. Then, the Chem3D program was employed to calculate minimum energy, and the structures were saved in SYBYL-2 (Mol2) format. The following enzymes were used: NADPH-oxidase (PDB ID: 2CDU, resolution at 1.80 Å); lipoxygenase (PDB ID: 1N8Q, resolution: 2.10 Å); xanthine oxidase (PDB ID: 3NRZ, resolution: 1.80 Å); and human cytochrome P450 CYP2C9 (PDB ID: 1OG5, resolution: 2.55 Å). These are closely related to antioxidant activity. Enzymes, obtained from the RCSB Protein Data Bank,¹ are 3D crystallographic configurations with excellent resolution based on X-ray diffraction. To optimize the protein structures, we applied Discovery Studio BIOVIA. Remaining and missing hydrogen atoms were included. Energy minimization was performed, and water molecules not required for ligand-binding or co-crystallization were eliminated (Gok et al., 2025). Swiss PDB Viewer 4.10 was then used to evaluate the final 3D structures of the target proteins.

Protein–ligand docking

The computer-generated browsing software interface of the AutoDockVina Tools version 4.2 was utilized to search the selected protein-ligand complex. Ligands were kept flexible throughout the search, while the protein was kept rigid (Edache et al., 2022). Then, the open babel tool integrated into the software stored protein structures and ligands in 'pdbqt' format. The active binding spot was enclosed within a grid box. The dimensions and coordinates were adjusted when observing the box boundary. AutoDock Vina uses the Lamarckian genetic algorithm for conformational searching. A semi-flexible docking technique was employed in this study. Subsequently, the database separates the combined energy and docking results into distinct conformers. Each protein and ligand conformer was then examined in Discovery Studio 2021 (Chi et al., 2025).

Molecular dynamics simulation

The optimal molecular docking results and their binding similarities within the active site of the target protein were assessed using a 100 ns molecular dynamics (MD) simulation. Structural dynamics of the complexes were analyzed on a Linux operating system by utilizing GROMACS version 2022 (Berendsen et al., 1995; Vieira et al., 2023). The CHARMM36 force field was generated using the CHARMM-GUI server's solution builder protocol (Croitoru et al., 2025), and the same interface was applied to create MDS recorded files in GROMACS. Each protein atom was molded in a periodic cubic box with a 10 Å and solvated using the previous TIP3P solutions. Counterions were inserted to ensure electroneutrality, and the Van der Waals interaction

¹ www.rcsb.org

was analyzed using the Verlet cutoff strategy with a value of 10α . The LINCS algorithm was used to restrict bonds (Hess et al., 1997). The particle mesh Ewald (PME) technique was applied to compute the electrostatic interactions (Sahasra et al., 2025). To minimize energy in the solvated systems, a steepest descent method was employed (Oviedo, 2022). First, the systems were equilibrated and maintained at constant levels using an NVT ensemble to fix constant temperature, volume, and particle count. A Python script included in the CHARMM-GUI was exploited to adapt GROMACS topology (top) and characteristics (itp) files for MDS within the GROMACS program, and the time step was set to 2 fs. The coordinates were then recorded at picosecond intervals for later review. To confirm accuracy of the computational predictions convergence tests and comparison with established computational standards were used to provide comprehensive validation of the consistency of MDS simulations of the MDS simulations.

MD simulation trajectory tests were used to evaluate the stability of the protein–ligand complex using RMSD analysis relative to the initial structure during the simulation.

The average difference between the protein–ligand combination, its original structure, and the stability of the complex during the simulation was evaluated using the RMSD measure. GROMACS tools were used to calculate RMSD values and track any structural changes, which were then displayed (Maruyama et al., 2023). The Rg value was calculated to validate the protein–ligand complex's efficiency and represents the mass distribution in relation to the system's center (Yamamoto et al., 2021). A constant Rg value represents stability in the structural integrity of the protein.

MM-PBSA analysis

To further validate molecular docking results, binding free energy determination for each protein–ligand pair was determined via MD/MM-PBSA calculation, and it was calculated by considering vacuum potential energy, which incorporates both bound and non-bonded interactions. The Poisson–Boltzmann equation was applied to determine the polar solvation energy component, while the SASA technique was employed to calculate the non-polar term, and the g_mmpbsa tool was employed for MM-PBSA computations to ensure compatibility with the GROMACS program (Ozen et al., 2025). The stability of MM-PBSA analysis was evaluated by comparing it with theoretical standards and consistency tests, thereby proving computational calculation of binding free energies during the simulation.

PASS analyses

This computational approach provides a reliable support for predicting numerous biological activities. The PASS online web server² was employed to predict compounds correlated with antioxidant activity at 90% precision. Correspondingly, the given chemical activities are considered probable only when $P_a > P_i$, and their rates vary between 0.000 and 1.000. $P_a > 0.7$ indicates superior activity, $0.7 > P_a > 0.5$ means normal activity, and $P_a < 0.5$ designates low activity. Furthermore, since they are calculated separately, $P_a + P_i$ value does not equal 1 (Basar et al., 2025). Figure 1 presents the

chemotype modulation, antioxidant responses, and molecular interactions of *S. officinalis* L. EO under drying temperature.

Statistical analysis

All assays were accomplished in triplicate, and data are expressed as mean $\pm$ standard deviation ($\pm$ SD). Data were analyzed using one-way analysis of variance (ANOVA), and differences were considered statistically significant at $p \leq 0.05$ (XLSTAT 2000).

Results and discussion

Essential oil yield and chemical and physical parameters

The EO obtained from fresh leaves was 0.16%, which corroborates with previously reported results (0.18%; Mahdjoubi et al., 2021). The dried *S. officinalis* leaves produced more EO than fresh ones (Figure 2). The maximum EO yield (0.29%) was obtained from leaves that were oven-dried at 50 °C, followed by freezing at -20 °C (0.24%), while oven-drying at 80 °C produced 0.20% (Figure 2; Imam et al., 2023).

Overall, compared with fresh plants, these results highlight that drying, particularly at low and moderate temperatures, can increase EO production ($p < 0.05$). These results indicate that higher temperatures may cause partial volatilization or degradation of essential oil components, while suggesting that preservation of plants at low and moderate temperatures maintains a substantial and probably enhances the release of volatile compounds without causing thermal degradation. This trend is consistent with previous studies indicating that EO content is sensitive to drying temperature (Bouteboulart et al., 2019; Mirahmadi et al., 2017; Sellami et al., 2011). These results reinforce previously documented studies on other aromatic plant species. For instance, Boukraa et al. (2021) showed that drying methods at 50 °C distinctly influence the extractability of *Mentha aquatic* L. EO.

Essential oil is typically pale yellow and characterized by a strong aromatic camphoraceous aroma. A noticeable color change was shown under drying temperature, with a yellow coloration in freezing samples and a darker yellow coloration in oven-dried samples, respectively (Figure 3). The viscosity of the EO has not been affected by drying temperature (Table 1).

The measured density ranged from 0.88 to 0.97, and the refractive index varied from 1.4338 to 1.4733 values complied with AFNOR standards and European Pharmacopeia (2020) standards, confirming the purity and quality of EO (Table 1).

These parameters are characterized by high quality of EO, which is rich in monoterpenes and oxygenated compounds, indicating minimal degradation or contamination during drying and extraction processes (Boukraa et al., 2024; Ferreira et al., 2021).

EO absorption spectra measured at different drying temperatures of the plants, recorded in the range of 200–400 nm, reveal characteristic absorption bands typical of complex mixtures of organic compounds (Figure 4). The spectrum displays strong absorption bands in the ultraviolet region, particularly between 200 and 280 nm, which may be attributed to electronic transitions commonly observed in aromatic rings and phenolic compounds (Casoni et al., 2024).

² <http://www.pharmaexpert.ru/passonline>

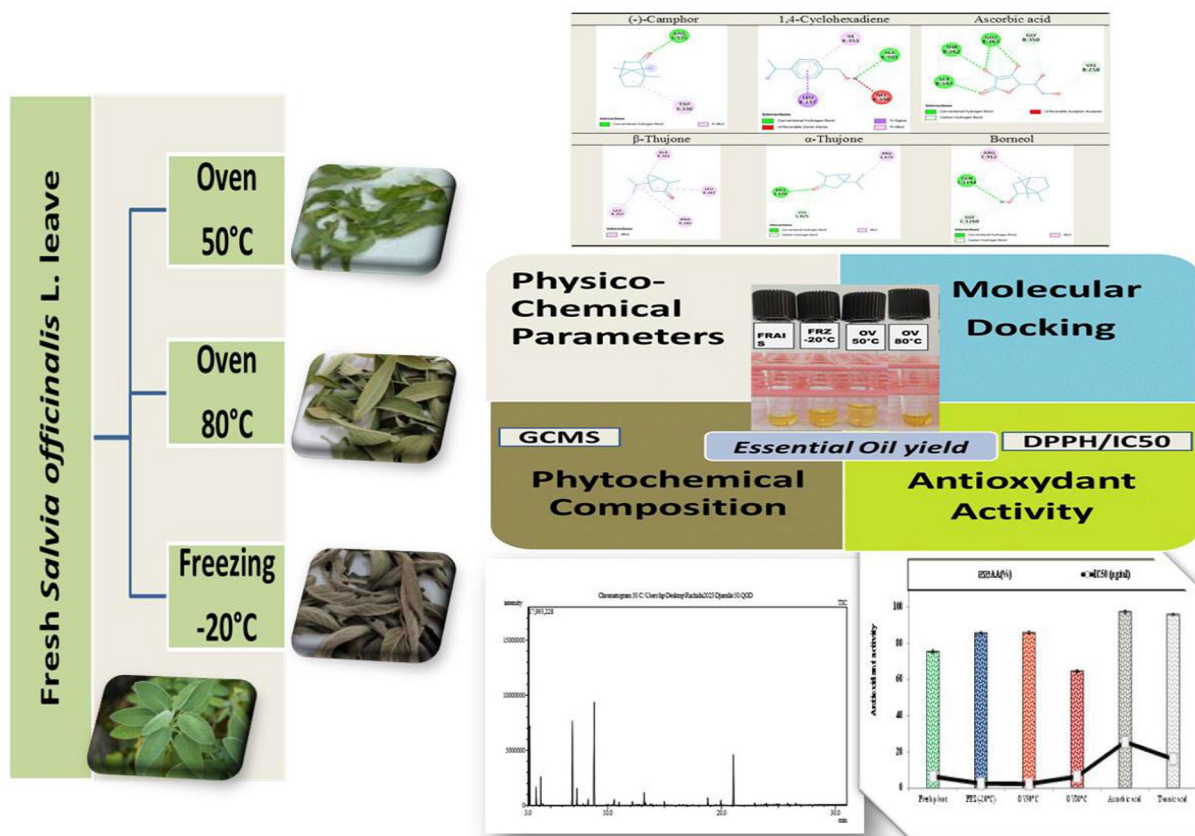


FIGURE 1

Chemotype modulation, antioxidant responses, and molecular interactions of *S. officinalis* L. EO under different drying temperatures.

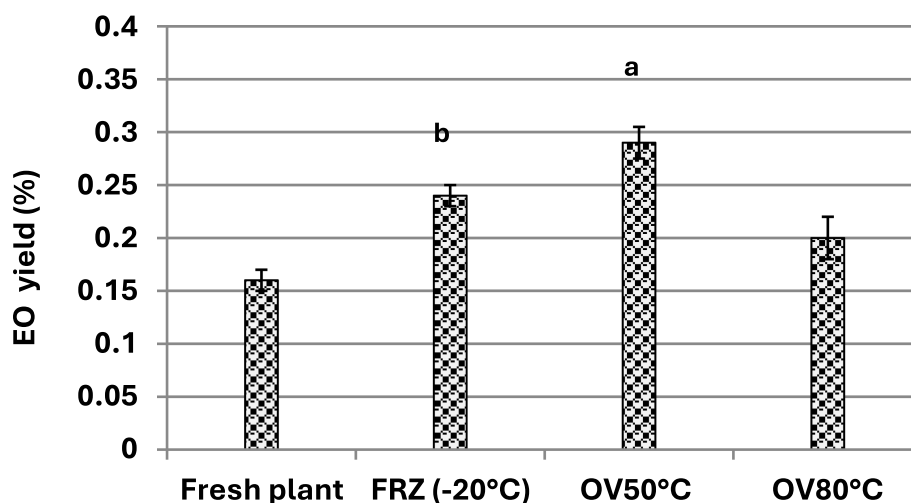


FIGURE 2

Different drying temperatures influenced EO yield (%).

The UV–Vis spectrum revealed the presence of chromophoric substances, notably phenolic derivatives, which contribute to biological activities, including antioxidant properties. Similar UV–Vis absorption characteristics have been documented in previous studies on EO enriched in monoterpenes and phenolic compounds, confirming the typical absorption behavior of such natural extracts (Huynh et al., 2020; Michiu et al., 2022).

Phytochemical constituents of *Salvia officinalis* EO

A total of 333, 343, and 357 substances were, respectively, identified in fresh EO, frozen EO, and dried EO at 50 °C (Figure 5).

As shown in Table 2, drying temperatures of *S. officinalis* exercises marked qualitative and quantitative variations in EO chemotype. EO

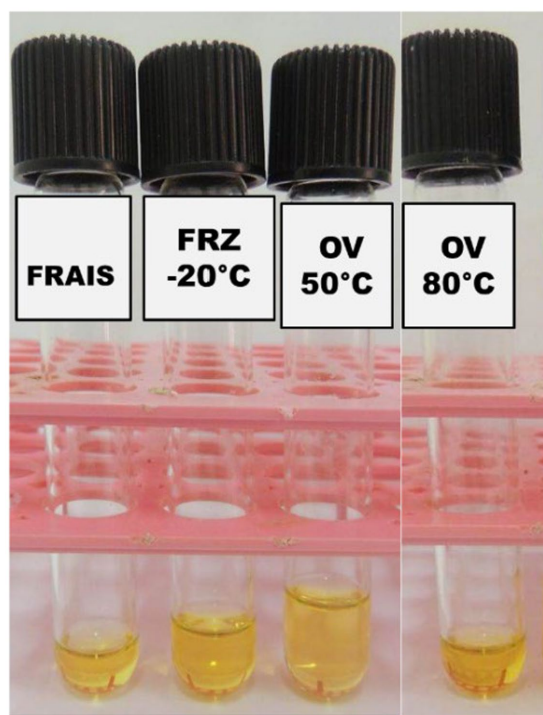


FIGURE 3
The EOs colors under different drying temperatures.

of fresh *S. officinalis* is characterized by a higher proportion of oxygenated monoterpenes, including α -thujone (15.64%), β -thujone (3.37%), camphor (18.50%), and epiglobulol (9.60%), reflecting a chemotype dominated by thujone, camphor derivatives, and minimal oxidative transformation.

Oven at 50 °C, in contrast, shows elevated levels of limonene (25.82%), humulene epoxide II (6.87%), and the appearance of p-cymene (3.17%), indicating that this drying condition enhances monoterpene oxidation and favors the formation of epoxide derivatives. β -Thujone and several sesquiterpenes are missing, which demonstrates higher thermal or oxidative breakdown. The freezing method presents elevated limonene and camphor levels (25.50 and 17.95%), respectively, and modest recovery of epiglobulol (6.61%), whereas sesquiterpenes, such as humulene and caryophyllene oxides, were detected again.

Generally, these results displayed that each drying temperature can considerably modulate the chemotype of *S. officinalis* EO, altering both the quantitative and qualitative aspects relative to its principal bioactive substances, including monoterpene hydrocarbons, monoterpene ketones, and sesquiterpenes.

Antioxidant activity

A notable inhibition value, ranging from 64 to 86%, has been exhibited by EO. Results indicate that essential oils derived from dried leaves at 50 °C and frozen leaves maintain a strong antioxidant activity (Baltacı et al., 2022). In contrast, 80 °C marked a decrease of around 65% compared with fresh plants (75%) (Durling et al., 2007). In addition, lower IC₅₀ values further confirm the superior antioxidant performance of *S. officinallis* EO compared to tannic acid and ascorbic acid (Figure 6).

According to previous interpretations, the presence of terpenoid compounds has been correlated with notable radical-scavenging

activity, as confirmed by related phytochemical and DPPH assays. Consequently, the UV–Vis spectral data provide valuable preliminary evidence supporting the biochemical richness and functional potential of the salvia essential oil. The spectral characteristics observed in the UV region are in agreement with the chemical composition generally reported for essential oils, which contain a high proportion of α -thujone (15.64%), β -thujone (3.37%), camphor, and sesquiterpene. These constituents are known for their high reactivity toward free radicals due to the presence of conjugated π -electron systems and hydroxyl functional groups (Huynh et al., 2020; Michiu et al., 2022).

Notably, these chemotype differences in EO also correlate with the change in antioxidant activity of *S. officinalis* conserved at different drying temperatures. The EO obtained from freezing and oven drying at OV50 °C was dominated by oxygenated monoterpenes, especially camphor, borneol, thujone isomers, and epiglobulol, and exhibited the highest RSA values ($\approx$ 84–86%), confirming that these molecules contribute significantly to radical scavenging capacity. In contrast, EO from fresh plants showed reduced RSA corresponding to a chemotype enriched in limonene and oxidized derivatives (p-cymene, humulene epoxide II), and a relative depletion of key antioxidant constituents.

These results demonstrated the direct influence of temperature levels induced chemotype variation on EO antioxidant potential.

When examining the relationship between chemical composition and antioxidant activity, a qualitative correlation can be observed between the main components and IC₅₀/RSA results. Specifically, the greatest antioxidant activity was observed in dried samples (50 °C) and (–20 °C), which were identified with higher levels of oxygenated monoterpenes such as camphor, borneol, and thujone derivatives. These compounds are commonly reported to exhibit strong radical scavenging activity due to the presence of oxygenated functional groups and enhanced redox potential (Kordali et al., 2005; Sürücü et al., 2025). Conversely, fresh sample which showed relatively lower antioxidant activity contain a higher proportion of limonene and fewer oxygenated compounds. Hydrocarbon monoterpenes, such as limonene, generally exhibit lower antioxidant activity compared to oxygenated terpenoids due to the absence of functional groups involved in electron-donating mechanisms (Badawy et al., 2019). This suggests that oxygenated terpenoids may play a more significant role than hydrocarbon monoterpenes in antioxidant performance (Sharifi-Rad et al., 2017).

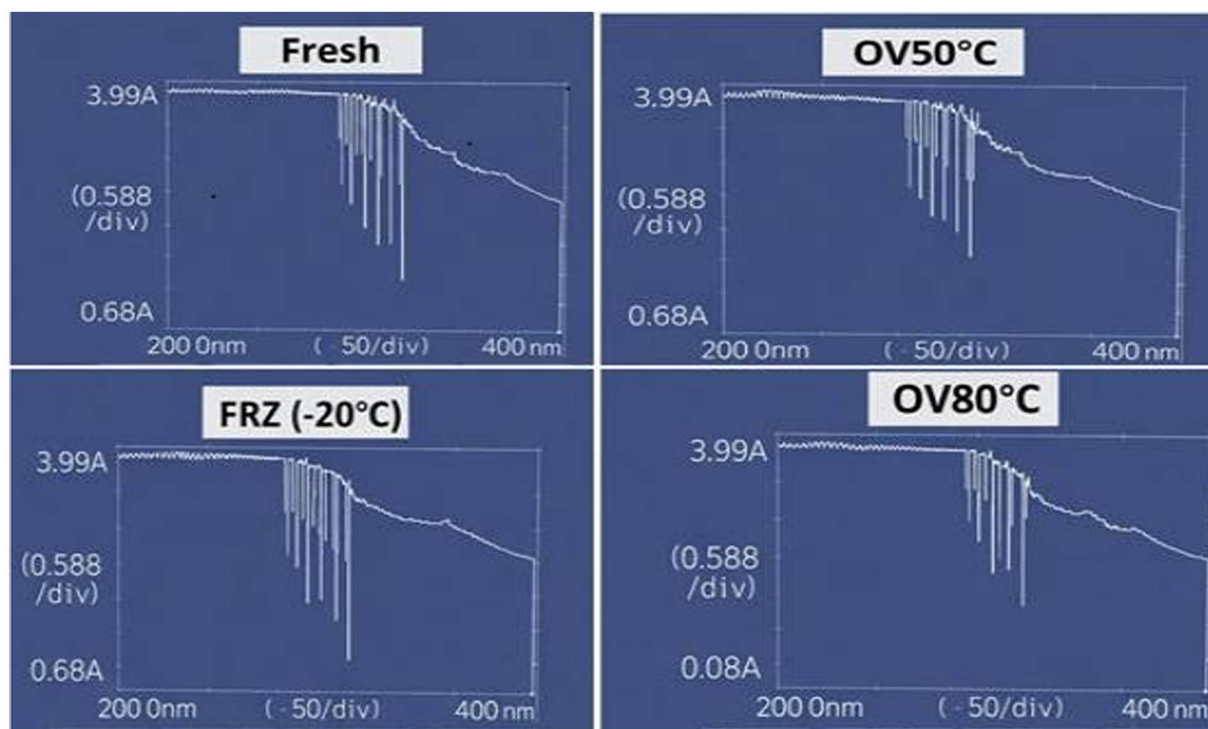
In silico analysis

Target protein selection was based on their known roles in oxidative stress-related pathways. Enzymes known as sources of reactive oxygen species (ROS), such as NADPH oxidase, lipoxygenase, and xanthine oxidase, are directly involved in oxidative processes (Jomova et al., 2025). In addition, cytochrome P450 enzymes, particularly CYP2C9, were included due to their roles in oxidative metabolism and their indirect contributions to redox homeostasis (Fekete et al., 2021). Although CYP2C9 (PDB ID: 1OG5) is not a classical antioxidant enzyme, it participates in the formation and detoxification of reactive intermediates, thus providing complementary information regarding oxidative stress modulation mechanisms (Martemucci et al., 2022; Van Booven et al., 2010).

Based on these experimental findings, an *in silico* study was conducted to further elucidate whether molecular docking results could support the predicted relationship between the chemical composition of *S. officinalis* EO and antioxidant potential. Theoretical calculations were performed on the interactions of the major compounds

TABLE 1 Impact of different drying temperatures on EO physico-chemical properties.

Samples	Color	Odor	Aspect	Density	Refractive indices
Fresh plant	Pale yellow	Strong camphoraceous	Viscous	0.94	1.47 ± 0.05
OV 50°C	Yellow	Strong camphoraceous	Viscous	0.90	1.46 ± 0.01
OV 80 °C	Yellow	Strong camphoraceous	Viscous	0.97	1.47 ± 0.00
FRZ (−20 °C)	Dark yellow	Strong camphoraceous	Viscous	0.88	1.44 ± 0.00
AFNOR standards (2000)	Yellow	Strong camphoraceous	Viscous	0.91–0.92	1.47 ± 0.00

FIGURE 4
Measurement of UV-Vis spectra between 200 and 400 nm of *S. officinalis* L. EO.

identified in *S. officinalis* EO obtained under different drying methods; these include (−)-camphor, 1,4-cyclohexadiene, β -thujone, α -thujon, borneol, caryophyllene, caryophyllene oxide, epiglobulol, eucalyptol, humulene, humulene epoxide II, isothimol methyl ether, limonene, β -cymene, and ascorbic acid.

Molecular docking results

The analysis of interactions of active sites of lipoxygenase enzyme revealed the presence of conventional hydrogen bonds, alkyl, π -alkyl, π -cation, and carbon–hydrogen bonds at amino acid residues ARG200, VAL144, and ASP158, respectively; and carbon–hydrogen bonds were observed at ALA163, GLU199, ASN164, VAL539, and ALA163. Alkyl interactions were observed at PHE155, VAL539, HIS548, ILE201, LYS545, ARG200, PHE161, VAL540, and TYR544. π -alkyl interactions were determined at the following residues: PHE155, VAL539, HIS548, PHE161, VAL540, VAL144, and TYR544. Furthermore, π -cation interactions were observed at LYS545 and GLU199 (Figure 7 and Supplementary Figure S1). When the binding energies were compared, epiglobulol (−7.8 kcal/mol) was determined to exhibit the highest binding energy. Furthermore, the binding

energy of all molecules except borneol (−5.6 kcal/mol) was higher than that of standard ascorbic acid (−5.7 kcal/mol) (Table 3).

It has been demonstrated that the interactions between molecules and active sites of P450 CYP2C9 include alkyl, π -alkyl, π -anion, π -sigma, and carbon–hydrogen bonds produced alkyl bonds with amino acid residues PRO367, LYS420, LYS322, ALA103, ALA106, LEU233, LEU208, VAL237, PRO346, PHE476, PRO367, LYS421, ARG342 and LEU366, as well as a π -alkyl bond with the amino acid residues PHE476, ALA103, PRO367, LEU366, PHE419, TYR347, LYS420, and PHE100. Typical hydrogen bonds were observed with amino acid residues, like GLY98, ARG433, ARG97, LEU366, SER365, ARG342, and GLU325, while PHE428, SER429, PRO367, and SER343 carbon–hydrogen bonds were observed. Also, π -anion interactions were determined with the amino acid residues ASP349 and PHE114 (Figure 7 and Supplementary Figure S2). Epiglobulol (−7.8 kcal/mol) exhibited the strongest binding affinity for the cytochrome P450 CYP2C9 enzyme. Furthermore, the binding energy of all molecules was calculated to be higher than that of ascorbic acid (−5.5 kcal/mol) (Table 3).

Alkyl bonds, π -alkyl bonds, π -sigma bonds, π -cation bonds, and π - π stacked interactions were observed when molecules interacted with the NADPH-oxidase enzyme. Accordingly, the following interactions with

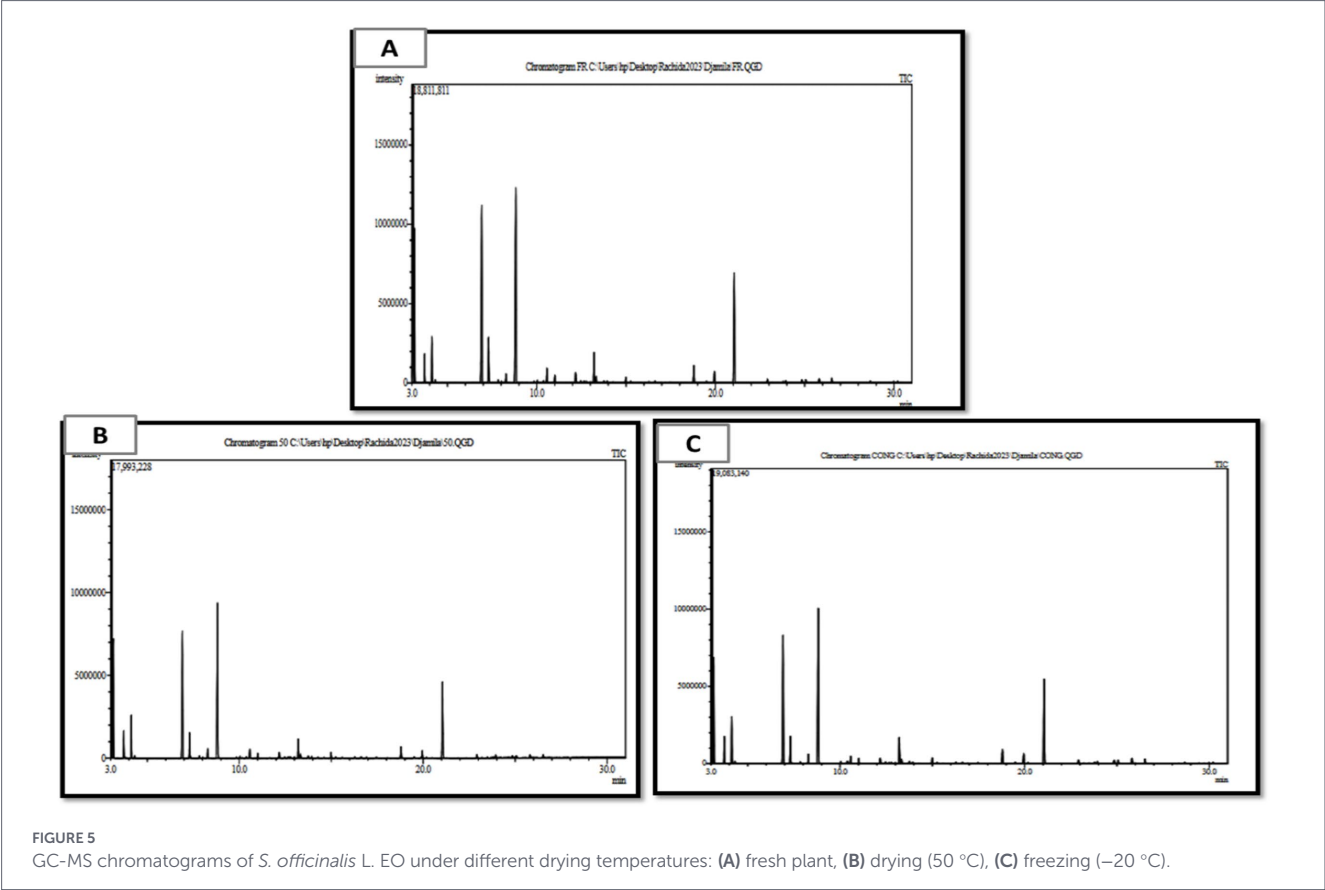


TABLE 2 Major compounds of *S. officinalis* L. essential oil (EO) (%).

No	Compounds (%)	R. T. min.	Fresh plant	Oven drying (50°C)	Freez-drying (−20 °C)
1	Limonene	3.081	19.95	25.82	25.52
2	Eucalyptol -	3.160	7.97	7.78	6.67
3	Gamma-Terpinene	3.724	1.56	2.00	1.89
4	P-Cymene	4.128	–	3.17	–
5	Isothymol methyl ether	4.130	2.62	–	3.35
6	α-Thujone	6.913	15.64	13.32	13.33
7	β-Thujone	7.304	3.37	–	2.67
8	(–)-Camphor	8.818	18.50	17.55	17.95
9	Caryophyllene	10.573	1.32	1.13	–
10	OxidCaryophyllene	18.795	1.59	1.51	1.72
11	Humulene	12.173	–	–	0.75
12	Epoxide Humulene II	19.948	1.11	6.87	1.25
13	Borneol	13.206	2.53	2.10	2.78
14	Epiglobulol	21.052	9.60	1.51	6.61

R. T, Retention Time.

amino acid residues were observed: alkyl interactions with VAL304, PRO432, ARG431, LYS17; π -alkyl interactions with HIS10, PHE14, PRO432, and TYR62; π - π stacked interactions with TYR62; and π -sigma interactions with HIS10 and TYR62. Additionally, HIS10, TYR62, PHE14, SER326, GLY341, SER328, TYR159, SER339, TYR188, ASN343, LYS187, and ARG431 amino acid residues were determined with conventional hydrogen bonds (Figure 7 and Supplementary Figure S3).

Epiglobulol (−7.9 kcal/mol) had the highest binding energy when the binding energies were compared (Table 3). Interactions involving alkyl, π -alkyl, π -cation, π -sigma, and carbon-hydrogen bonds were observed between molecules and the xanthine oxidase enzyme. The following amino acid residues were observed to form conventional hydrogen bonds: ARG335, ALA301, THR262, GLU2363, SER347, MET826, GLN1194, ARG37, while were observed

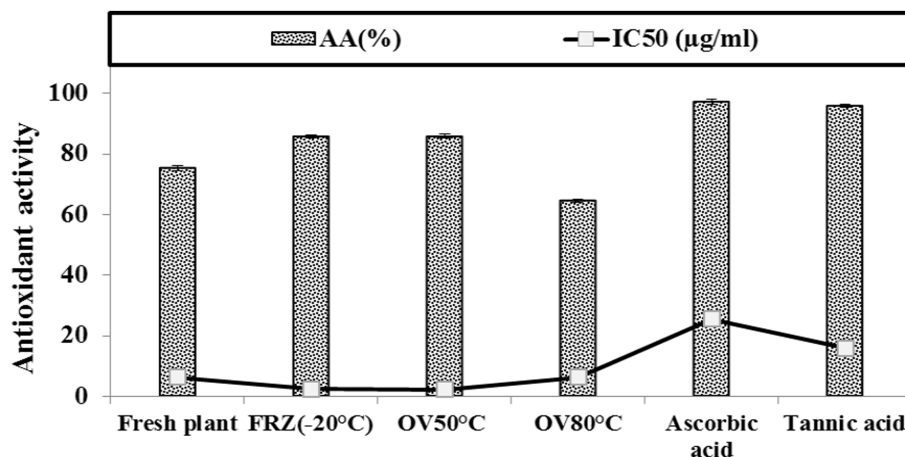


FIGURE 6

Impact of different drying temperatures on EO antioxidant activity (%) and IC₅₀ value (µg/ml).

to form carbon hydrogen bonds; GLY350, VAL258, CYS825, GLY1260, GLY820, HIS683, GLY349, ALA301. Also ALA301, PRO281, LEU257, LEU287, PRO675, ARG912, PRO597, LEU157, MET1038, ILE353, LEU398, ILE403, VAL259, VAL591, ILE596, LYS754, ILE752, LYS792 were observed to form alkyl interactions while TYR599, LYS754 and VAL591 π -alkyl interactions were observed. Furthermore, π -sigma interactions were observed with LEU257, and π -cation interactions were observed with LYS754 (Figure 7 and Supplementary Figure S4). When the binding energies were compared, it was found that Epiglobulol exhibited the highest combining energy (-8.7 kcal/mol) (Table 3). Furthermore, Epiglobulol had the highest binding energy against all enzymes studied. We therefore performed a 100-ns MD simulation to confirm its inhibitory properties against xanthine oxidase, the enzyme against which Epiglobulol has the highest attachment energy. In general, hydrocarbon monoterpenes exhibit moderate binding affinity, while oxygenated terpenoids tend to display stronger interactions with target enzymes. This suggests that biological activity depends not only on compound abundance but also on molecular structure and functional groups. Therefore, the relationship between chemical composition and binding outcomes should be considered a qualitative trend rather than a precise quantitative correlation. Additionally, although the analysis primarily considered the parent compounds, secondary components may also contribute to overall antioxidant activity through synergistic or additive effects. Therefore, the observed antioxidant activity may result from synergistic interactions among multiple components rather than the action of individual compounds.

Findings obtained in a computer environment provide supporting information for the experimentally observed antioxidant activity. Compounds such as epiglobulol, cariophyllene oxide, and humulene derivatives, which exhibit strong binding tendencies to enzymes involved in oxidative stress, may contribute to the modulation of reactive oxygen species (ROS) generating pathways. This observation is consistent with experimental results showing that samples rich in oxygenated terpenoids exhibit enhanced radical scavenging activity. In this context, *in silico* analyses have been considered a complementary approach to support and elucidate the possible mechanisms of antioxidant activity observed *in vitro*.

To further validate and refine molecular docking findings, molecular dynamics (MD) breeding was performed in conjunction with MM-PBSA analysis to calculate stability and protein–ligand complexes

binding free energies under dynamic conditions. MD simulations were investigated to study conformational and functional dynamics of the protein (Roosan et al., 2025). MD modeling can be used to explore protein dynamics, folding, stability, and ligand–protein interactions. Different molecular docking and MD simulations in this study verified the stability of the compound with XO complexes in physiological contexts (Lat et al., 2024). By examining RMSD plots, RMSF, gyrate, SASA, H-bonds, and binding free energy, the MD simulations ascertained that complexes are consistent with the target protein (XO) and Epiglobulol.

Root mean square deviation

Figure 8 shows a complex RMSD plot and ligands co-crystallized with the XO protein. The complex stabilized at around 5 nm for the following time periods: 0–6 ns, 17–28 ns, 28–32 ns, 34–72 ns, 74–76 ns, 83–87 ns, and 90–92 ns. At other times, the RMSD values reached approximately 17.5 nm. The protein and its components were fixed at about 5 nm for 100 ns. High RMSD indicates the flexibility of the complex structure.

Root mean square fluctuation

The RMSF results estimate the variance around the average site of each deposit. The higher RMSF values reflect enhanced residue conformational flexibility and can be used to facilitate the identification of structurally flexible or rigid sites of the protein. According to Figure 5, XO protein forms a more stable product at approximately 0.25 nm, which suggests that the structure is kept flexible, indicating its structural compactness during the simulation.

Lower Rg value signifies a protein with a folded or compact structure, whereas a higher Rg value denotes an unfolded structure. Figure 5 illustrates XO Rg values with an average value of 4.59 nm, indicating that the Rg profile maintains its mechanical compactness during the modulation of each compound.

Hydrogen bonds analysis

Figure 6 presents, on average, three H-bonds were formed at XO target spots. It clearly shows that the complexes preserve the H-bond

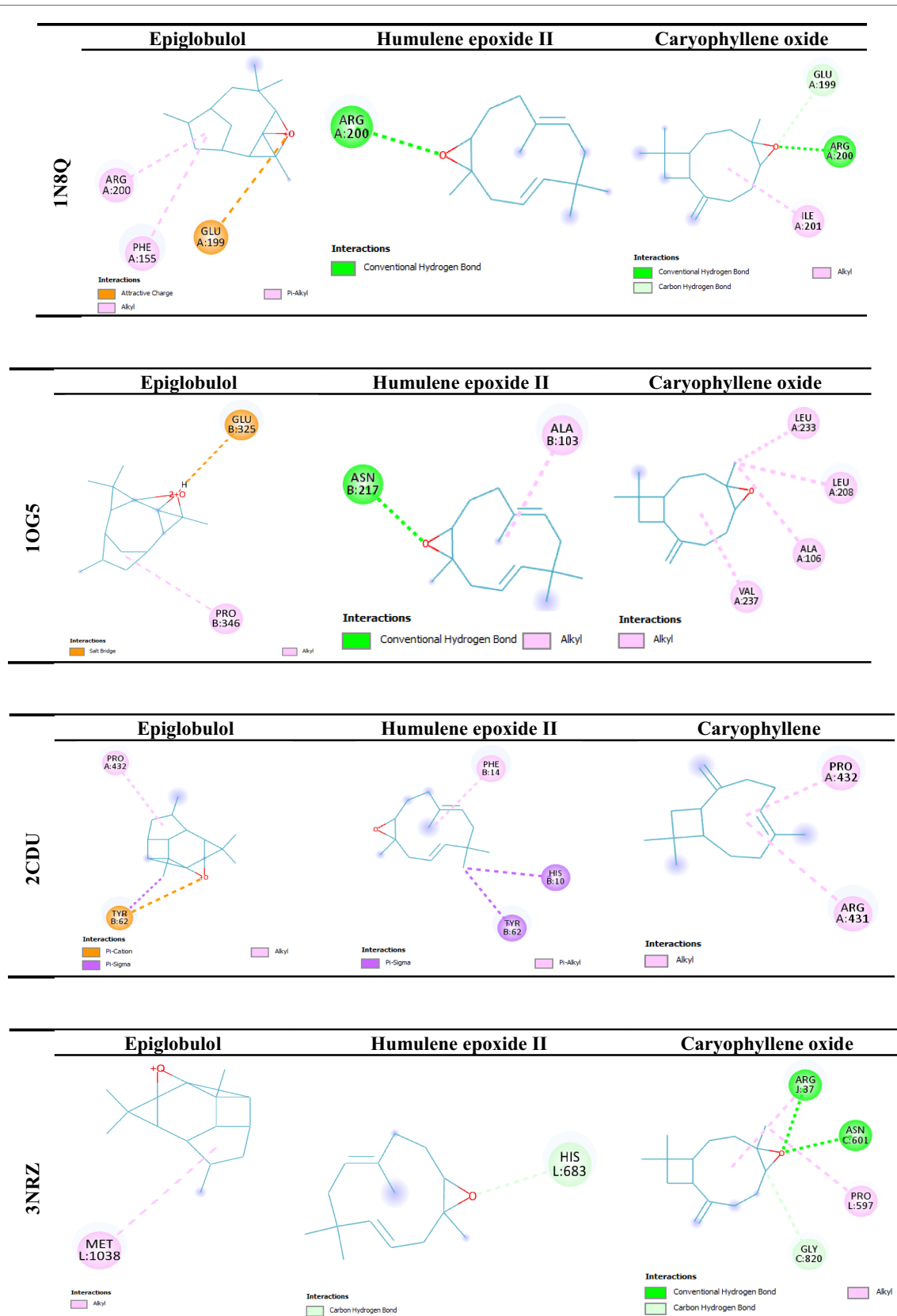


FIGURE 7
2D images of the interactions of the main components in *S. officinalis* EO with 1N8Q, 1OG5, 2CDU, and 3NRZ.

created between the ligand and amino acids during the 100-ns simulation. This observation corroborates evaluations of earlier structural studies, suggesting stability upon interaction with the XO protein throughout the simulation.

SASA refers to the surface area of protein that is accessible to exposed solvent. XO protein–ligand interactions, folding, ligand binding, or conformational changes indicate variations in this parameter. SASA values are 0.25 nm², 900 nm² and 900 nm² for compound, protein,

TABLE 3 Binding energy values of the interactions of proteins and ligands (kcal/mol).

Molecules/standards	1N8Q	1OG5	2CDU	3NRZ
(-)-Camphor	-5.7	-6.1	-5.7	-5.3
1,4-Cyclohexadiene	-6.3	-5.9	-6.2	-6.3
β-Thujone	-6.1	-6.0	-6.1	-6.4
α-Thujone	-6.1	-6.0	-6.2	-5.6
Borneol	-5.6	-5.7	-5.7	-6.1
Caryophyllene	-6.9	-7.4	-7.4	-6.6
Caryophyllene oxide	-7.6	-7.6	-7.3	-7.2
Epiglobulol	-7.8	-7.8	-7.9	-8.7
Eucalyptol	-5.9	-5.8	-5.9	-5.9
Humulene	-6.9	-7.3	-7.4	-6.6
Humulene epoxide II	-7.6	-7.6	-7.5	-6.8
Isothymol methyl ether	-6.1	-6.1	-6.3	-6.5
Limonene	-6.0	-6.2	-6.1	-6.4
p-Cymene	-6.2	-6.1	-6.1	-6.5
Ascorbic acid	-5.7	-5.5	-6.5	-6.2

Where 1N8Q: Lipoxygenase, 1OG5: cytochrome P450 CYP2C9, 2CDU: NADPH-oxidase, 3NRZ: xanthine oxidase.

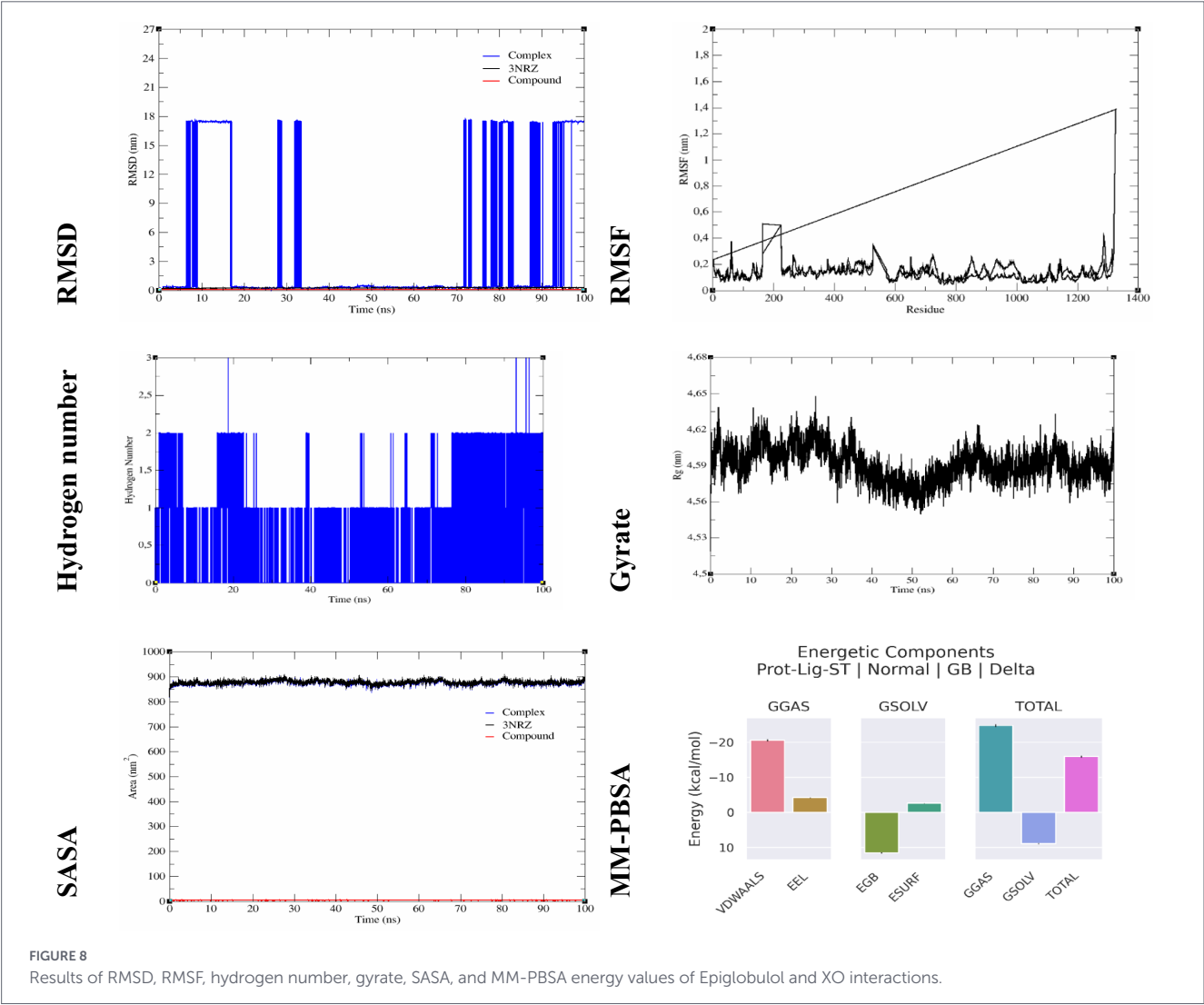


TABLE 4 Computation MM/PBSA calculation of compounds and enzymes interaction (kcal/mol).

Samples	VDWAALS	EEL	EGB	E _{surf}	ΔG _{gas}	ΔG _{solv}	Total
Epiglobulol	−20.60 ± 0.31	−4.21 ± 0.08	11.53 ± 0.18	−2.62 ± 0.04	−24.81 ± 0.38	8.91 ± 0.14	−15.90 ± 0.25

VDWAALS (Van der Waals contribution from MM), EEL (electrostatic energy as calculated by the MM force field), EGB (the electrostatic contribution to the solvation-free energy calculated by GB), E_{surf} (hydrophobic contribution to solvation-free energy for GB calculations), ΔG_{gas} (total gas phase energy (ELE + VDW + INT)), ΔG_{solv} (sum of nonpolar and polar contributions to solvation), Total (ΔG_{binding}).

and complex, respectively (Figure 6). Simulation displayed minimal variation attributed to lower structural complexity alterations.

The Epiglobulol-XO complex exhibited satisfactory stable complex formation. SASA analysis complemented the RMSD, RMSF, and Rg results, providing further clarification on the correlation between interactions of compounds' stability with the XO target protein related to antioxidant effect.

Molecular mechanics–Poisson–Boltzmann surface area

MM-PBSA computation allows the estimation of binding strengths and evaluates the energetic stability of protein–ligand complex. GROMACS used gmxmmpbsa implementation to compute ligand–protein free energy interactions. Docked complex determination of XO target area and compound, as well as binding free energy for the complex, was completed using Equation 5.

$$\Delta G_{\text{bind}} = G_{\text{complex}} - (G_{\text{protein}} + G_{\text{ligand}}) \quad (5)$$

Table 4 illustrates calculations results for other energies, such as van der Waals energy, electrostatic energy, polar solvation energy, and non-polar solvation energy. Based on the obtained results, polar solvation energy presents a positive value that indicates no contribution, whereas E_{vdW}, E_{ele}, and G_{non-polar}, with negative values, make a considerable contribution.

The compound was shown to interact efficiently inside active sites of XO, with the compound exhibiting binding energies of (−15.90 kcal/mol) (Table 4).

Although molecular docking, molecular dynamics, and MM-PBSA present important insights into preliminary information on protein-binding interactions, their predictive capacity remains limited in evaluating the full complexity of biological processes. Factors such as bioavailability, metabolic transformations, and conformational flexibility of proteins are not fully represented in these models. Therefore, the results obtained should be considered not as definitive proof of biological activity, but as complementary and supportive findings contributing to mechanistic interpretations. Therefore, additional *in vitro* and *in vivo* experiments are required to validate these findings.

PASS-based biological activity spectra prediction analysis

PASS software programmer uses the structure–activity interaction of a well-identified chemical compound to predict its antioxidant activity, including phytochemicals, as well as desired pharmacological effect, such as teratogenicity, embryotoxicity, carcinogenicity, mutagenicity, and embryotoxicity (Jamkhande et al., 2016). Biological activity is evaluated as potential activity (Pa) and potential inactivity (Pi). Just structures with Pa greater than Pi were retained for each pharmacological activity. Data were interpreted based on the following scoring scheme. Probable

activity was considered as high when Pa > 0.7, likely with 0.5 < Pa < 0.7, and as low when Pa < 0.5 (Başar et al., 2025). PASS analysis results showed that all molecules exhibited cytochrome P450 (CYP₂) substrate activity. This suggests that these molecules have the ability to initiate antioxidant mechanisms (Supplementary Table S1).

Conclusion

Drying temperature plays a pivotal role in modeling yield, phytochemical contents, and antioxidant capacity of essential oils of *S. officinalis*. Moderate temperature (50 °C) and low temperature (−20 °C) significantly preserved both rate and chemical integrity, and exclusively maintained antioxidant activity comparable to that of fresh material. In contrast, higher drying temperatures induced thermal degradation of the volatile compound. Chemotype variation among essential oils was closely associated with differences in antioxidant performance. Molecular docking computation further supported these findings by showing that all major molecules exhibit cytochrome P450₂ (CYP₂) binding activity involved in antioxidant processes. Collectively, this study provides valuable insight into how post-harvest management directly influences the antioxidant parameters of EO and underlines the importance of optimized drying protocols to ensure high-quality EO suitable for pharmaceutical and cosmetic usages.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Author contributions

DB: Methodology, Conceptualization, Writing – original draft. RacA: Methodology, Investigation, Writing – review & editing. YB: Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. ST: Methodology, Software, Writing – review & editing. NT: Methodology, Data curation, Writing – original draft. TF: Methodology, Formal analysis, Writing – review & editing. AAA: Methodology, Project administration, Writing – original draft. RawA: Methodology, Validation, Writing – review & editing. AMA: Methodology, Resources, Writing – original draft. HB: Methodology, Writing – original draft, Visualization. AA: Methodology, Writing – original draft, Investigation. MH: Methodology, Writing – original draft, Software. SA: Methodology, Writing – original draft, Data curation. RS: Methodology, Supervision, Writing – review & editing.

Funding

The author(s) declared that financial support was received for this work and/or its publication. The study was supported by Deanship of Graduate Studies and Scientific Research, Taif University.

Acknowledgments

The authors gratefully acknowledge the support of the Deanship of Graduate Studies and Scientific Research, Taif University, for funding this study.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that Generative AI was not used in the creation of this manuscript.

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fsufs.2026.1818527/full#supplementary-material>

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